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**14. ABSTRACT** The objective of this study was to establish whether metabolic syndrome plays a role in the progression of prostate cancer and the influence of metabolic syndrome and/or its individual features on the progression of prostate cancer between African American men (AAM) and European American men (EAM). From our results we conclude that both hypertension and metabolic syndrome (defined by possessing 3 of the 4 measured features) are associated with high Gleason grade disease at the time of diagnosis among EAM (but not among AAM). We also conclude that hypertension and diabetes are associated with increased risk for biochemical recurrence and again the relationship appears stronger for EAM than it is for AAM. Further we suggest from these findings that metabolic syndrome and its features among AAM may be associated with early prostate cancer (early in the natural history of the disease). This would be consistent with case-control reports of metabolic syndrome. A recent Swedish report of European men with metabolic syndrome found no evidence of an association between high levels of metabolic factors and the risk of prostate cancer, but high BMI, elevated blood pressure and a composite score of all metabolic factors were associated with an increase risk of death from prostate cancer. These reports are similar to our findings. The totality of the evidence seems to suggest that the biology of prostate cancer is different between AAM and EAM, where features of metabolic syndrome are associated with prostate cancer risk (initiation) in AAM they seem to be associated with progression of disease in EAM.

**15. SUBJECT TERMS**

The influence of metabolic syndrome on prostate cancer progression and recurrence

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## Introduction

Prostate cancer (PCa) mortality is approximately 2.5 times higher in African American men (AAM) than European American men (EAM) (1). However, it has been reported that when PCa is pathologically organ confined, there is no difference in time until biochemical recurrence (BCR), but if the cancer is pathologically non-organ confined or locally advanced, risk of BCR recurrence is greater in AAM compared to EAM (2). It is likely that both genetic and epigenetic factors contribute significantly to racial/ethnic disparity in PCa risk and progression. Metabolic syndrome (MetSyn) is a cluster of conditions that served as risk factors for cardiovascular disease with insulin resistance as the defining feature. A working definition developed by the National cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) is commonly used to characterize individuals as having MetSyn. Persons who possess at least 3 of the following 5 features are classified as having MetSyn: 1) abdominal obesity (waist circumference of  $> 102$  cm in men or  $> 88$  cm in women); 2) hypertriglyceridemia ( $\geq 150$  mg/dl); 3) low high-density lipoprotein (HDL) cholesterol ( $< 40$  mg/dl in men and  $< 50$  mg/dl in women); 4) high blood pressure ( $\geq 130/85$  mm Hg); and 5) high fasting glucose  $\geq 110$  mg/dl. We hypothesize that MetSyn plays a significant role in the aggressiveness and biochemical recurrence of PCa among AAM and may contribute significantly to disparity in outcome among AAM compared to EAM. Our specific aims include 1) To examine the association between specific features of metabolic syndrome and the development of aggressive versus non-aggressive PCa in AAM and EAM; and 2) To examine the association between specific features of MetSyn PCa recurrence among AAM and EAM.

## BODY

### Introduction

Prostate cancer mortality is approximately 2.5 times higher in black men than in white men [1]. However, it has been reported that when prostate cancer is pathologically organ confined, there is no difference in biochemical recurrence, but if the cancer is pathologically non-organ confined or locally advanced, risk of biochemical recurrence is greater in blacks compared to whites [2]. It is likely that both genetic and epigenetic factors contribute significantly to racial/ethnic disparity in prostate cancer risk and progression.

Metabolic syndrome is a cluster of conditions that served as risk factors for cardiovascular disease with insulin resistance as the defining feature. A working definition developed by the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) is commonly used to characterize individuals as having metabolic syndrome. Persons who possess at least three of the following five features are classified as having metabolic syndrome: 1) abdominal obesity (waist circumference of  $>102$  cm in men or  $>88$  cm in women), 2) hypertriglyceridemia ( $\geq 150$  mg/dL), 3) low high-density lipoprotein (HDL) cholesterol ( $< 40$  mg/dL in men and  $<50$  mg/dL in women), 4) high blood pressure ( $\geq 130/85$  mm Hg) and 5) high fasting glucose  $\geq 110$  mg/dL.

Metabolic syndrome is prevalent in the United States as it has been estimated that it is present in approximately 30%-35% of adults over the age of 18 years [3]. Certain racial and ethnic groups are predisposed to developing specific features of metabolic syndrome. Whites present most frequently with lipid abnormalities (hypertriglyceridemia and low HDL cholesterol), blacks and Asians present with hypertension whereas diabetes is diagnosed most often among Hispanics, Pacific Islanders and Native Americans [4]. The prevalence of obesity in the United States has increased dramatically over the past four decades, irrespective of race and ethnicity with approximately one-third of adults characterized as obese (BMI  $\geq 30$  kg/m<sup>2</sup>) [5].

Several reports including our own indicate a relationship between metabolic syndrome and prostate cancer [6-13]. However, few have sought to examine the relationship between metabolic syndrome and aggressive prostate cancer or risk of disease progression or biochemical recurrence particularly in a racially diverse patient population. Beebe-Dimmer et al observed that metabolic syndrome, using a definition consistent with ATP III, was associated with prostate cancer risk in black men, but not white men. Furthermore, no association was observed between either metabolic syndrome, or any of its individual features, with aggressive prostate cancer phenotype.[13] Yet, two independent investigations of men with prostate cancer treated with radical prostatectomy suggest that hypertension was associated with an increased risk for biochemical recurrence even after adjustment for other metabolic syndrome features [14,15]. The intriguing observed associations represent a first step in the understanding the relationship between metabolic syndrome and prostate cancer risk and progression.

## KEY RESEARCH ACCOMPLISHMENTS

We projected total recruitment for the Metabolic Syndrome Study of 500 patients approximately 50% of which would be black. We recruited a total of 473 patients, ~65% of which were black (n=309) with a total response rate of approximately 85%. The total number of patients included in the analysis for this report include those patients who completed both survey, anthropometric measures and have had clinical data abstracted for electronic medical records (n=426). For the remaining 47 patients, we are currently abstracting clinical information for our database. Analysis for all subsequent manuscripts will include the total number of enrolled patients.

## Results

Table 1 presents demographic characteristics and health behaviors of prostate cancer patients participating in the study. Approximately 60% of patients were married at the time of diagnosis, however white patients were much more likely to be married (82%) compared to black patients (43%). White patients were also more educated than black with nearly 50% of whites reported at least a college degree compared to ~24% of blacks. ~30% of patients reported a family history of prostate cancer in first and/or second degree relatives. Black men were more likely to report having smoked and were more likely than whites to be current smokers at the time of diagnosis. White patients were more likely than blacks to report having consumed alcohol in the prior month (65% vs. 45%). Whites were also more likely than blacks to report having at least one PSA test prior to their pre-diagnostic PSA test (83% vs. 55%).

**Table 1. Demographic Characteristics and Health Behaviors among Prostate Cancer Patients Participating in Metabolic Syndrome Study.**

| Variable                                 | White<br>N = 154<br>n (%) | Black<br>N = 272<br>n (%) | Total<br>N = 426<br>n (%) |
|------------------------------------------|---------------------------|---------------------------|---------------------------|
| <b>Marital status</b>                    |                           |                           |                           |
| Married                                  | 127 (82.47)               | 122 (44.85)               | 249 (58.45)               |
| Divorced/Separated                       | 16 (10.39)                | 89 (32.72)                | 105 (24.65)               |
| Widowed                                  | 3 (1.95)                  | 22 (8.09)                 | 25 (5.87)                 |
| Never Married                            | 8 (5.20)                  | 39 (14.34)                | 47 (11.03)                |
| <b>Education</b>                         |                           |                           |                           |
| Less than High School                    | 6 (3.90)                  | 51 (18.96)                | 57 (13.48)                |
| High School                              | 30 (19.48)                | 71 (26.39)                | 101 (23.88)               |
| Some College                             | 39 (25.32)                | 78 (29.00)                | 117 (27.66)               |
| College Degree                           | 41 (26.62)                | 46 (17.10)                | 87 (20.57)                |
| Professional Degree                      | 33 (21.43)                | 18 (6.69)                 | 51 (12.06)                |
| Other                                    | 5 (3.25)                  | 5 (1.86)                  | 10 (2.36)                 |
| <b>Family History of Prostate Cancer</b> |                           |                           |                           |
| No                                       | 107 (69.93)               | 191 (71.27)               | 298 (70.78)               |
| Yes                                      | 46 (30.07)                | 77 (28.73)                | 123 (29.22)               |

|                                         |            |             |             |
|-----------------------------------------|------------|-------------|-------------|
| <b>Ever Smoked</b>                      |            |             |             |
| No                                      | 66 (42.86) | 100 (36.76) | 166 (38.97) |
| Yes                                     | 88 (57.14) | 172 (63.24) | 260 (61.03) |
| <b>Current Smoker</b>                   |            |             |             |
| No                                      | 73 (82.96) | 102 (59.30) | 175 (67.31) |
| Yes                                     | 15 (17.04) | 70 (40.70)  | 85 (32.69)  |
| <b>Alcohol Intake in the Past Month</b> |            |             |             |
| No                                      | 55 (35.71) | 150 (55.15) | 205 (48.12) |
| Yes                                     | 99 (64.29) | 122 (44.85) | 221 (51.88) |
| <b>No. of Alcohol Servings</b>          |            |             |             |
| 0-1 per week                            | 33 (34.02) | 38 (33.63)  | 71 (33.81)  |
| 2-3 per week                            | 30 (30.93) | 39 (34.51)  | 69 (32.86)  |
| 4-6 per week                            | 9 (9.28)   | 11 (9.74)   | 20 (9.52)   |
| one per day                             | 13 (13.40) | 9 (8.00)    | 22 (10.48)  |
| 2+ per day                              | 12 (12.37) | 16 (14.16)  | 28 (13.33)  |
| <b>Alcohol Consumed</b>                 |            |             |             |
| beer                                    | 42 (42.42) | 51 (42.15)  | 93 (42.27)  |
| wine                                    | 31 (31.31) | 23 (19.01)  | 54 (24.55)  |
| liquor                                  | 22 (22.22) | 38 (31.40)  | 60 (27.27)  |
| combination of the above                | 4 (4.04)   | 9 (7.44)    | 13 (5.91)   |

| Variable                             | White<br>N = 154<br>n (%) | Black<br>N = 272<br>n (%) | Total<br>N = 426<br>n (%) |
|--------------------------------------|---------------------------|---------------------------|---------------------------|
| <b>Usual Alcohol Intake</b>          |                           |                           |                           |
| No                                   | 26 (16.99)                | 36 (13.43)                | 62 (14.73)                |
| Yes                                  | 127 (83.01)               | 232 (86.57)               | 359 (85.27)               |
| <b>Usual No. of Alcohol Servings</b> |                           |                           |                           |
| 0-1 per week                         | 16 (61.54)                | 26 (74.29)                | 42 (68.85)                |
| 2-3 per week                         | 5 (19.23)                 | 3 (8.57)                  | 8 (13.11)                 |
| 4-6 per week                         | 3 (11.54)                 | 4 (11.43)                 | 7 (11.48)                 |
| one per day                          | 1 (3.85)                  | 0 (0.00)                  | 1 (1.64)                  |
| 2+ per day                           | 1 (3.85)                  | 2 (5.71)                  | 3 (4.92)                  |
| <b>Prior PSA Testing</b>             |                           |                           |                           |
| No                                   | 26 (16.88)                | 122 (44.85)               | 148 (34.74)               |
| Yes                                  | 128 (83.12)               | 150 (55.15)               | 278 (65.26)               |
| <b>Prior PSA Result</b>              |                           |                           |                           |
| normal                               | 87 (73.11)                | 85 (64.39)                | 172 (68.53)               |
| abnormal                             | 32 (26.89)                | 47 (35.61)                | 79 (31.47)                |

Table 2 summarizes the clinical and treatment characteristics on participants. About 60% of patients were diagnosed with Gleason score 7 and higher based upon biopsy findings. 28% of patients were treated with radiation therapy while nearly 60% were treated with radical prostatectomy. Six percent of patients

had lymph node invasion at diagnosis and less than 1% presenting with metastatic disease. However, 19% of patients had evidence of biochemical recurrence and nearly 7% of patients eventually developed metastatic disease.

**Table 2. Clinical Characteristics of Prostate Cancer Patients Participating in the Metabolic Syndrome Study.**

| Variable                                       | White<br>N = 154<br>n (%) | Black<br>N = 272<br>n (%) | Total<br>N = 426<br>n (%) |
|------------------------------------------------|---------------------------|---------------------------|---------------------------|
| <b>Biopsy Gleason Score</b>                    |                           |                           |                           |
| 6                                              | 50 (33.11)                | 104 (38.52)               | 154 (36.58)               |
| 7                                              | 63 (41.72)                | 113 (41.85)               | 176 (41.81)               |
| 8                                              | 20 (13.25)                | 28 (10.37)                | 48 (11.4)                 |
| 9                                              | 17 (11.26)                | 23 (8.52)                 | 40 (9.50)                 |
| 10                                             | 1 (0.66)                  | 2 (0.74)                  | 3 (0.71)                  |
| <b>Radiation Therapy</b>                       |                           |                           |                           |
| No                                             | 106 (72.11)               | 187 (71.37)               | 293 (71.64)               |
| Yes                                            | 41 (27.89)                | 75 (28.63)                | 116 (28.36)               |
| <b>Prostatectomy</b>                           |                           |                           |                           |
| No                                             | 57 (38.0)                 | 111 (41.57)               | 168 (40.29)               |
| Yes                                            | 93 (62.0)                 | 156 (58.43)               | 249 (59.71)               |
| <b>Pathology Tumor Stage</b>                   |                           |                           |                           |
| T2                                             | 11 (14.47)                | 21 (16.67)                | 32 (15.84)                |
| T2a                                            | 3 (3.95)                  | 7 (5.56)                  | 10 (4.95)                 |
| T2b                                            | 2 (2.63)                  | 2 (1.59)                  | 4 (1.98)                  |
| T2c                                            | 28 (36.84)                | 55 (43.65)                | 83 (41.09)                |
| T2x                                            | 3 (3.95)                  | 4 (3.175)                 | 7 (3.47)                  |
| T3                                             | 2 (2.63)                  | 2 (1.59)                  | 4 (1.98)                  |
| T3a                                            | 14 (18.42)                | 22 (17.46)                | 36 (17.82)                |
| T3b                                            | 13 (17.11)                | 13 (10.32)                | 26 (12.87)                |
| <b>Pathology Nodes stage</b>                   |                           |                           |                           |
| NX                                             | 10 (13.89)                | 15 (12.93)                | 25 (13.3)                 |
| N0                                             | 57 (79.17)                | 94 (81.03)                | 151 (80.32)               |
| N1                                             | 5 (6.94)                  | 7 (6.03)                  | 12 (6.38)                 |
| <b>Metastatic Disease at time of Diagnosis</b> |                           |                           |                           |
| MX                                             | 85 (92.39)                | 136 (90.67)               | 221 (91.32)               |
| M0                                             | 7 (7.61)                  | 13 (8.67)                 | 20 (8.26)                 |
| M1                                             | 0 (0.00)                  | 1 (0.67)                  | 1 (0.41)                  |
| <b>Pathology Gleason Score</b>                 |                           |                           |                           |
| 6                                              | 31 (34.83)                | 56 (36.60)                | 87 (35.95)                |

|                               |            |             |             |
|-------------------------------|------------|-------------|-------------|
| 7                             | 39 (43.82) | 82 (53.59)  | 121 (50.00) |
| 8                             | 10 (11.24) | 12 (7.84)   | 22 (9.09)   |
| 9                             | 8 (8.99)   | 3 (1.96)    | 11 (4.55)   |
| 10                            | 1 (1.12)   | 0 (0.00)    | 1 (0.41)    |
|                               |            |             |             |
| <b>Extent of Disease</b>      |            |             |             |
| Clinically Localized          | 90 (58.44) | 188 (69.12) | 278 (65.26) |
| Locally Advanced              | 51 (33.12) | 69 (25.37)  | 120 (28.17) |
| Metastatic                    | 13 (8.44)  | 15 (5.52)   | 28 (6.57)   |
|                               |            |             |             |
| <b>Biochemical Recurrence</b> |            |             |             |
| No                            | 85 (79.44) | 168 (81.95) | 253 (81.09) |
| Yes                           | 22 (20.56) | 37 (18.05)  | 59 (18.91)  |
|                               |            |             |             |

Table 3 summarizes the metabolic syndrome characteristics of participants. Black patients were more likely than white patients to report both having high blood pressure (75% versus 58%) and high blood sugar or diabetes (28% versus 19%). White patients were more likely to report having high cholesterol (63% versus 54%). Forty percent of participants were obese, with a slightly higher proportion of white patients with a body mass index (BMI) greater than 30 kg/m<sup>2</sup>. Abdominal obesity measured through the use of measured waist circumference was more prevalent in white patients (62%) compared to black patients (48%). Approximately 31% of patients were classified as having metabolic syndrome using measured BMI to classify obesity and metabolic syndrome defined as possessing any 3 of the 4 measured features (obesity, hypertension, diabetes, hypercholesterolemia). If waist circumference was used to measure obesity, the prevalence of metabolic syndrome among study participants was 35% and slightly higher among black patients than white.

**Table 3. Metabolic Syndrome Characteristics among Prostate Cancer Patients in the Metabolic Syndrome Study.**

| Variable                           | White<br>N=154<br>n (%) | Black<br>N = 272<br>n (%) | Total<br>N = 426<br>n (%) |
|------------------------------------|-------------------------|---------------------------|---------------------------|
| <b>High Blood Pressure</b>         |                         |                           |                           |
| No                                 | 64 (41.83)              | 67 (24.63)                | 131 (30.82)               |
| Yes                                | 89 (58.17)              | 205 (75.37)               | 294 (69.18)               |
| <b>High Blood Sugar/Diabetes</b>   |                         |                           |                           |
| No                                 | 124 (81.05)             | 193 (71.75)               | 317 (75.12)               |
| Yes                                | 29 (18.95)              | 76 (28.25)                | 105 (24.88)               |
| <b>High Cholesterol</b>            |                         |                           |                           |
| No                                 | 56 (36.84)              | 121 (46.01)               | 177 (42.65)               |
| Yes                                | 96 (63.16)              | 142 (53.99)               | 238 (57.35)               |
| <b>BMI &gt; 30kg/m<sup>2</sup></b> |                         |                           |                           |
| No                                 | 87 (58.39)              | 161 (60.98)               | 248 (60.05)               |

|                                         |             |              |             |
|-----------------------------------------|-------------|--------------|-------------|
| Yes                                     | 62 (41.61)  | 103 (39.02)  | 165 (39.95) |
|                                         |             |              |             |
| <b>Waist circumference &gt; 40in</b>    |             |              |             |
| No                                      | 47 (38.21)  | 123 ( 51.90) | 170 (47.22) |
| Yes                                     | 76 (61.79)  | 114 ( 48.10) | 190 (52.78) |
|                                         |             |              |             |
| <b>Metabolic Syndrome (using BMI)</b>   |             |              |             |
| No                                      | 108 (73.47) | 169 (66.80)  | 277 (69.25) |
| Yes                                     | 39 (26.53)  | 84 (33.20)   | 123 (30.75) |
|                                         |             |              |             |
| <b>Metabolic Syndrome (using Waist)</b> |             |              |             |
| No                                      | 81 (66.94)  | 145 (63.60)  | 226 (64.76) |
| Yes                                     | 40 (33.06)  | 83 (36.40)   | 123 (35.24) |
|                                         |             |              |             |

**Table 4A. Odds ratios for aggressive disease in association with each specific feature of metabolic syndrome and with metabolic syndrome, for all patients.**

| Aggressive Disease Definition<br>and<br>Metabolic Syndrome feature | Odds ratio (OR), 95% Confidence Intervals (CI) and p-values |               |         |                          |               |         |
|--------------------------------------------------------------------|-------------------------------------------------------------|---------------|---------|--------------------------|---------------|---------|
|                                                                    | Unadjusted OR                                               |               |         | Adjusted OR <sup>a</sup> |               |         |
|                                                                    | OR                                                          | 95% CI        | p-value | OR                       | 95% CI        | p-value |
| <b>Aggressive Disease <sup>b</sup></b>                             |                                                             |               |         |                          |               |         |
| High Blood Pressure                                                | 0.761                                                       | (0.50 - 1.17) | 0.2095  | 0.828                    | (0.53 - 1.29) | 0.4023  |
| High Blood Sugar                                                   | 0.613                                                       | (0.38 - 1.00) | 0.0500  | 0.661                    | (0.40 - 1.09) | 0.1021  |
| High Cholesterol                                                   | 0.856                                                       | (0.57 - 1.29) | 0.4551  | 0.811                    | (0.53 - 1.23) | 0.3277  |
| Obesity                                                            | 0.721                                                       | (0.47 - 1.09) | 0.1241  | 0.658                    | (0.43 - 1.02) | 0.0582  |
| Metabolic Syndrome <sup>c</sup>                                    | 0.716                                                       | (0.45 - 1.13) | 0.1502  | 0.735                    | (0.46 - 1.17) | 0.1918  |
|                                                                    |                                                             |               |         |                          |               |         |
| <b>Aggressive Gleason Grade <sup>d</sup></b>                       |                                                             |               |         |                          |               |         |
| High Blood Pressure                                                | 1.329                                                       | (0.85 - 2.08) | 0.2113  | 1.427                    | (0.90 - 2.28) | 0.1356  |
| High Blood Sugar                                                   | 1.197                                                       | (0.75 - 1.90) | 0.4462  | 1.210                    | (0.75 - 1.94) | 0.4295  |
| High Cholesterol                                                   | 0.951                                                       | (0.63 - 1.44) | 0.8099  | 0.889                    | (0.58 - 1.36) | 0.5846  |
| Obesity                                                            | 1.066                                                       | (0.70 - 1.62) | 0.7635  | 1.081                    | (0.70 - 1.66) | 0.7228  |
| Metabolic Syndrome                                                 | 1.233                                                       | (0.79 - 1.93) | 0.3580  | 1.250                    | (0.79 - 1.97) | 0.3373  |

|  |  |  |  |  |  |  |
|--|--|--|--|--|--|--|
|  |  |  |  |  |  |  |
|--|--|--|--|--|--|--|

- a Adjusted for age at diagnosis, race, and having a prior PSA test (yes/no).  
b Extent of Disease considered to be either locally advanced or metastatic disease compared to localized disease.  
c Any 3 of the 4 measured metabolic syndrome features.  
d Biopsy Gleason score 4 + 3 and higher compared to 3+4 and lower.

**Table 4B. Odds ratios for aggressive disease in association with each specific feature of metabolic syndrome and with Metabolic Syndrome, for African-American patients.**

| Aggressive Disease Definition<br>and<br>Metabolic Syndrome Feature | Odds ratio (OR), 95% Confidence Intervals and p-values |               |         |                          |               |         |
|--------------------------------------------------------------------|--------------------------------------------------------|---------------|---------|--------------------------|---------------|---------|
|                                                                    | Unadjusted OR                                          |               |         | Adjusted OR <sup>a</sup> |               |         |
|                                                                    | OR                                                     | 95% CI        | p-value | OR                       | 95% CI        | p-value |
| <b>Aggressive Disease <sup>b</sup></b>                             |                                                        |               |         |                          |               |         |
| High Blood Pressure                                                | 0.571                                                  | (0.32 - 1.02) | 0.0561  | 0.586                    | (0.33 - 1.05) | 0.0727  |
| High Blood Sugar                                                   | 0.737                                                  | (0.41 - 1.33) | 0.3128  | 0.777                    | (0.43 - 1.41) | 0.4089  |
| High Cholesterol                                                   | 0.533                                                  | (0.31 - 0.91) | 0.0200  | 0.527                    | (0.31 - 0.90) | 0.0194  |
| Obesity                                                            | 0.540                                                  | (0.31 - 0.94) | 0.0305  | 0.507                    | (0.29 - 0.90) | 0.0199  |
| Metabolic Syndrome <sup>c</sup>                                    | 0.545                                                  | (0.30 - 0.99) | 0.0478  | 0.566                    | (0.31 - 1.04) | 0.0649  |
|                                                                    |                                                        |               |         |                          |               |         |
| <b>Aggressive Gleason Grade <sup>d</sup></b>                       |                                                        |               |         |                          |               |         |
| High Blood Pressure                                                | 1.166                                                  | (0.63 - 2.15) | 0.6209  | 1.100                    | (0.59 - 2.06) | 0.7659  |
| High Blood Sugar                                                   | 1.023                                                  | (0.58 - 1.82) | 0.9381  | 0.977                    | (0.54 - 1.76) | 0.9372  |
| High Cholesterol                                                   | 0.886                                                  | (0.52 - 1.50) | 0.6508  | 0.816                    | (0.48 - 1.40) | 0.4615  |
| Obesity                                                            | 1.174                                                  | (0.69 - 2.00) | 0.5569  | 1.258                    | (0.73 - 2.19) | 0.4147  |
| Metabolic Syndrome                                                 | 1.212                                                  | (0.69 - 2.13) | 0.5039  | 1.178                    | (0.66 - 2.10) | 0.5794  |
|                                                                    |                                                        |               |         |                          |               |         |

- a Adjusted for age at diagnosis, race, and having a prior PSA test (yes/no).  
b Extent of Disease considered to be either locally advanced or metastatic disease compared to localized disease.  
c Any 3 of the 4 measured metabolic syndrome features.  
d Biopsy Gleason score 4 + 3 and higher compared to 3+4 and lower.

**Table 4C. Odds ratios for aggressive disease in association with each specific feature of metabolic syndrome and with Metabolic Syndrome, for white patients.**

| Aggressive Disease Definition<br>and<br>Metabolic Syndrome Feature | Odds ratio (OR) and associated statistics |               |         |                          |               |         |
|--------------------------------------------------------------------|-------------------------------------------|---------------|---------|--------------------------|---------------|---------|
|                                                                    | Unadjusted OR                             |               |         | Adjusted OR <sup>a</sup> |               |         |
|                                                                    | OR                                        | 95% CI        | p-value | OR                       | 95% CI        | p-value |
| <b>Aggressive disease <sup>b</sup></b>                             |                                           |               |         |                          |               |         |
| High Blood Pressure                                                | 1.300                                     | (0.67 - 2.51) | 0.4337  | 1.285                    | (0.66 - 2.51) | 0.4636  |
| High Blood Sugar                                                   | 0.478                                     | (0.20 - 1.16) | 0.1032  | 0.469                    | (0.19 - 1.15) | 0.0970  |
| High Cholesterol                                                   | 1.648                                     | (0.83 - 3.26) | 0.1521  | 1.656                    | (0.82 - 3.36) | 0.1617  |
| Obesity                                                            | 1.042                                     | (0.54 - 2.01) | 0.9013  | 0.962                    | (0.49 - 1.91) | 0.9113  |
| Metabolic Syndrome <sup>c</sup>                                    | 1.200                                     | (0.57 - 2.51) | 0.6276  | 1.115                    | (0.53 - 2.35) | 0.7756  |
|                                                                    |                                           |               |         |                          |               |         |
|                                                                    |                                           |               |         |                          |               |         |
| <b>Aggressive Gleason Grade <sup>d</sup></b>                       |                                           |               |         |                          |               |         |
| High Blood Pressure                                                | 1.911                                     | (0.97 - 3.77) | 0.0621  | 2.006                    | (.999 - 4.03) | 0.0503  |
| High Blood Sugar                                                   | 1.923                                     | (0.84 - 4.41) | 0.1224  | 1.889                    | (0.82 - 4.36) | 0.1361  |
| High Cholesterol                                                   | 0.956                                     | (0.48 - 1.90) | 0.8977  | 1.058                    | (0.52 - 2.14) | 0.8748  |
| Obesity                                                            | 0.889                                     | (0.45 - 1.74) | 0.7317  | 0.906                    | (0.45 - 1.83) | 0.7818  |
| Metabolic Syndrome                                                 | 1.383                                     | (0.65 - 2.92) | 0.3959  | 1.499                    | (0.70 - 3.23) | 0.3016  |
|                                                                    |                                           |               |         |                          |               |         |

a Adjusted for age at diagnosis, race, and having a prior PSA test (yes/no).

b Extent of Disease considered to be either locally advanced or metastatic disease compared to localized disease.

c Any 3 of the 4 measured metabolic syndrome features.

d Biopsy Gleason score 4 + 3 and higher compared to 3+4 and lower.

**Table 5A. Hazard ratios for biochemical recurrence<sup>a</sup> in association with each specific feature of metabolic syndrome and with Metabolic Syndrome, for all 312 patients combined.**

| Metabolic Syndrome feature | Hazard ratio (HR) and associated statistics |               |         |                          |               |         |
|----------------------------|---------------------------------------------|---------------|---------|--------------------------|---------------|---------|
|                            | Unadjusted HR                               |               |         | Adjusted HR <sup>b</sup> |               |         |
|                            | HR                                          | 95% CI        | p-value | HR                       | 95% CI        | p-value |
| High Blood Pressure        | 1.610                                       | (0.79 - 3.30) | 0.1924  | 1.462                    | (0.68 - 3.14) | 0.3294  |
| High Blood Sugar           | 1.539                                       | (0.88 - 2.69) | 0.1293  | 1.369                    | (0.78 - 2.41) | 0.2775  |
| High Cholesterol           | 0.925                                       | (0.54 - 1.59) | 0.7785  | 0.869                    | (0.50 - 1.52) | 0.6208  |
| Obesity                    | 0.930                                       | (0.53 - 1.63) | 0.7997  | 1.126                    | (0.63 - 2.00) | 0.6864  |

|                           |       |               |        |       |               |        |
|---------------------------|-------|---------------|--------|-------|---------------|--------|
| <b>Metabolic Syndrome</b> | 1.447 | (0.82 - 2.55) | 0.2008 | 1.407 | (0.79 - 2.50) | 0.2459 |
|                           |       |               |        |       |               |        |

<sup>a</sup> Endpoint for analysis was the time from biopsy date until the first date of biochemical recurrence (defined as a PSA > 4.0 ng/mL). Of the 312 patients, 59 (19%) had biochemical recurrence.

The 253 patients (81%) who never had a follow-up PSA > 4.0 ng/mL were censored for recurrence as of the date of their most recent PSA determination.

The HR is estimated from a Cox regression model. The effective sample sizes for any given Cox model are slightly smaller due to occasional missing data on the given Met Syn exposure variable and/or on a covariate(s).

<sup>b</sup> Adjusted for age at diagnosis, race (AA or EA), biopsy Gleason score in 3 groups ( < 7, 3+4, or [4+3 or > 7] ), and having a prior PSA test ( yes/no ).

**Table 5B. Hazard ratios for biochemical recurrence<sup>a</sup> in association with each specific feature of metabolic syndrome and with Metabolic Syndrome for 205 African American (AA) patients.**

| <b>Metabolic Syndrome feature</b> | <b>Hazard ratio (HR) and associated statistics</b> |               |         |                                |               |         |
|-----------------------------------|----------------------------------------------------|---------------|---------|--------------------------------|---------------|---------|
|                                   | <b>Unadjusted HR</b>                               |               |         | <b>Adjusted HR<sup>b</sup></b> |               |         |
|                                   | HR                                                 | 95% CI        | p-value | HR                             | 95% CI        | p-value |
| <b>High Blood Pressure</b>        | 1.033                                              | (0.43 - 2.49) | 0.9428  | 0.846                          | (0.34 - 2.12) | 0.7219  |
| <b>High Blood Sugar</b>           | 1.319                                              | (0.67 - 2.60) | 0.4226  | 1.266                          | (0.63 - 2.53) | 0.5047  |
| <b>High Cholesterol</b>           | 1.493                                              | (0.75 - 2.97) | 0.2530  | 1.354                          | (0.66 - 2.78) | 0.4090  |
| <b>Obesity</b>                    | 0.861                                              | (0.44 - 1.68) | 0.6610  | 0.996                          | (0.50 - 1.98) | 0.9915  |
| <b>Metabolic Syndrome</b>         | 1.531                                              | (0.78 - 3.02) | 0.2179  | 1.443                          | (0.73 - 2.88) | 0.2966  |
|                                   |                                                    |               |         |                                |               |         |

<sup>a</sup> Endpoint for analysis was the time from biopsy date until the first date of biochemical recurrence (defined as a PSA > 4.0 ng/mL). Of the 205 AA patients, 37 (18%) had biochemical recurrence.

The 168 AA patients (82%) who never had a follow-up PSA > 4.0 ng/mL were censored for recurrence as of the date of their most recent PSA determination.

The HR is estimated from a Cox regression model. The effective sample sizes for any given Cox model are slightly smaller due to occasional missing data on the given Met Syn exposure variable and/or on a covariate(s).

<sup>b</sup> Adjusted for age at diagnosis, biopsy Gleason score in 3 groups ( < 7, 3+4, or [4+3 or > 7] ), and having a prior PSA test ( yes/no ).

**Table 5C. Hazard ratios for biochemical recurrence<sup>a</sup> in association with each specific feature of metabolic syndrome and with Metabolic Syndrome, for 107 European American (EA) patients.**

| <b>Metabolic Syndrome feature</b> | <b>Hazard ratio (HR) and associated statistics</b> |              |         |                                |               |         |
|-----------------------------------|----------------------------------------------------|--------------|---------|--------------------------------|---------------|---------|
|                                   | <b>Unadjusted HR</b>                               |              |         | <b>Adjusted HR<sup>b</sup></b> |               |         |
|                                   | HR                                                 | 95% CI       | p-value | HR                             | 95% CI        | p-value |
| <b>High Blood Pressure</b>        | 3.261                                              | (0.94-11.28) | 0.0618  | 2.500                          | (0.68 - 9.13) | 0.1657  |

|                           |       |               |        |       |               |        |
|---------------------------|-------|---------------|--------|-------|---------------|--------|
| <b>High Blood Sugar</b>   | 2.246 | (0.84 - 6.01) | 0.1071 | 1.486 | (0.51 - 4.35) | 0.4702 |
| <b>High Cholesterol</b>   | 0.368 | (0.14 - 0.95) | 0.0397 | 0.397 | (0.15 - 1.07) | 0.0666 |
| <b>Obesity</b>            | 1.158 | (0.42 - 3.20) | 0.7775 | 1.635 | (0.54 - 5.00) | 0.3885 |
| <b>Metabolic Syndrome</b> | 1.336 | (0.46 - 3.85) | 0.5918 | 1.251 | (0.40 - 3.96) | 0.7036 |
|                           |       |               |        |       |               |        |

<sup>a</sup> Endpoint for analysis was the time from biopsy date until the first date of biochemical recurrence (defined as a PSA > 4.0 ng/mL). Of the 107 EA patients, 22 (21%) had biochemical recurrence. The 85 EA patients (79%) who never had a follow-up PSA > 4.0 ng/mL were censored for recurrence as of the date of their most recent PSA determination. The HR is estimated from a Cox regression model. The effective sample sizes for any given Cox model are slightly smaller due to occasional missing data on the given Met Syn exposure variable and/or on a covariate(s).

<sup>b</sup> Adjusted for age at diagnosis, biopsy Gleason score in 3 groups ( < 7, 3+4, or [4+3 or > 7] ), and having a prior PSA test ( yes/no ).

Tables 4a-4c summarize findings related to Specific Aim I of the study, namely to examine the relationship between features of metabolic syndrome with aggressive prostate cancer. For these analyses, we selected to variable to classify aggressive disease. The first measure was based on extent of disease (EOD) in 3 categories, clinically localized disease, locally advanced disease and metastatic. The latter two categories were combined. The second measure was based on biopsy Gleason grade, comparing patients with 4+3 and higher grade with 3+4 and lower. Our data suggest that both hypertension alone and metabolic syndrome are associated with high Gleason grade at time of diagnosis. Furthermore, the relationship between these conditions and Gleason grade appears stronger for white patients compared to black. There was no consistent relationship between metabolic syndrome features and EOD, in fact there was some suggestion that metabolic syndrome was inversely related to EOD among black patients.

Tables 5a-5c summarize findings related to Specific Aim II of the study namely to examine the relationship between features of metabolic syndrome with biochemical recurrence among radical prostatectomy patients. Our data suggest that hypertension and diabetes were associated with an increased risk for biochemical recurrence, and again the relationship appeared stronger for white patients compared to black patients.

## OUTCOMES

### A. Abstracts

Beebe-Dimmer, J., Powell, I., Podgorski, I., Bock, C., Bolton, S., Lewis, S., Heilbrun, L. The Influence of Metabolic Syndrome on Prostate Cancer Progression and Risk of Recurrence in African-American and European-American Men. *Submission to DoD for IMPACT meeting.*

### B. Presentations

Beebe-Dimmer, J. The Influence of Metabolic Syndrome on Prostate Cancer Progression and Risk of Recurrence in African-American and European-American Men. The U.S. Department of Defense (DoD) Prostate Cancer Research Program (PRCP) IMPACT meeting. Orlando, Florida. March, 2011.

**C. Funded Grants**

PI: Izabela Podgorski

Title: Biochemical and Genetic Markers in Aggressiveness and Recurrence of Prostate Cancer: Race-Specific Links to Inflammation and Insulin Resistance

Funding Agency: Department of Defense

Direct Costs: \$342,000

Study Period: 07/01/10-06/30/13

PI: Cathryn Bock

Title: Reducing Racial Disparities in Prostate Cancer Aggressiveness, Recurrence and Quality of Life

Funding Agency: Fund for Cancer Research

Direct Costs: \$100,000

Study Period: 07/01/12- 06/30/13

**D. Pending Grants**

PI: Cathryn Bock

Title: MicroRNA and the MicroRNA biosynthesis pathway in Prostate Cancer Racial Disparities and Aggressiveness

Funding Agency: Department of Defense

Direct Costs: \$450,000

1/1/13-12/31/15

**E. Submitted Grants (not funded)**

PI: Cathryn Bock

Title: The Role of MicroRNA in Prostate Cancer Racial Disparities and Aggressiveness

Funding Agency: National Cancer Institute

Direct Costs: \$ 1,383,208

PI: Cathryn Bock

Title: Reducing Racial Disparities in Prostate Cancer Aggressiveness, Recurrence and Quality of Life

Funding Agency: Department of Defense

Direct Costs: \$450,000

**CONCLUSIONS**

The objective of this study was to establish whether metabolic syndrome plays a role in the progression of prostate cancer and the influence of metabolic syndrome and/or its individual features on the progression of prostate cancer between African American men (AAM) and European American men (EAM). From our results we conclude that both hypertension and metabolic syndrome (defined by possessing 3 of the 4 measured features) are associated with high Gleason grade disease at the time of diagnosis among EAM (but not among AAM). We also conclude that hypertension and diabetes are associated with increased risk for biochemical recurrence and again the relationship appears stronger for EAM than it is for AAM. Further we suggest from these findings that metabolic syndrome and its features among AAM may be associated with early prostate cancer (early in the natural history of the disease). This would be

consistent with case-control reports of metabolic syndrome specifically hypertension and obesity (12,13) that find that these features are associated with prostate cancer risk of diagnosis (prostate cancer carcinogenesis) among AAM. A recent Swedish report of European men with metabolic syndrome found no evidence of an association between high levels of metabolic factors and the risk of prostate cancer, but high BMI, elevated blood pressure and a composite score of all metabolic factors were associated with an increase risk of death from prostate cancer. These reports are similar to our findings. The totality of the evidence seems to suggest that the biology of prostate cancer is different between AAM and EAM, where features of metabolic syndrome are associated with prostate cancer risk (initiation) in AAM they seem to be associated with progression of disease in EAM.

Further investigation of the biology and genetics of prostate cancer and specific genes and biological pathways associated with metabolic syndrome and specifically hypertension need to be conducted. In fact we have investigated gene expression and biological pathways of molecular factors associated with metabolic syndrome such as inflammatory cytokines, ALOX12 and 15, and AKT. There is evidence that Angiotension II associated with hypertension induces the release of inflammatory cytokines and reactive oxygen species that interact with arachidonic acid and cause mutation of AKT that ultimately activates androgen receptor which causes prostate cancer cell proliferation. Our results of this separate study previously funded by DOD are preliminary. We will be seeking funds to further investigate the apparent biological differences between AAM and EAM to establish specific biomarkers and targeted biological therapy.

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